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10/561,529

05/30/2006

Fabrizio Samaritani

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WOODARD, EMHARDT, MORIARTY, MCNETT & HENRY LLP  
111 MONUMENT CIRCLE, SUITE 3700  
INDIANAPOLIS, IN 46204-5137

EXAMINER

STOICA, ELLY GERALD

ART UNIT

PAPER NUMBER

1647

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/561,529	<b>Applicant(s)</b> SAMARITANI ET AL.	
	<b>Examiner</b> ELLY-GERALD STOICA	<b>Art Unit</b> 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10/01/2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 24-58 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 24-58 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>09/29/2008</u>  | 6) <input type="checkbox"/> Other: _____                          |

**DETAILED ACTION**

**Response to amendment**

***Status of the claims***

1. In the amendment filed on 10/01/2008, Applicant cancelled the previous claims 1-23 and added the new claims 24-58, which are now pending and subject to examination. The new claims generally comprise a reorganization of the prior pending claims.
2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

***New claim rejections necessitated by amendment***

***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 24-41 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by De Meere et al. (U. S. Pat. No. 5,384,132- cited by Applicant).

De Meere et al. disclosed lyophilized gonadotropin containing preparations containing a dicarboxylic acid salt stabilizer. The particular proteins (e.g. LH, TSH, FSH, or HCG) are in admixture with, and at least partially capable of stabilization by, the particular stabilizer in lyophilized form. The preparations preferably include a non-

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reducing disaccharide to increase the collapse temperature of the solution to be lyophilized. Methods of making the preparations in lyophilized form and the resulting injectable preparations are also disclosed (Abstract). Follicle stimulating hormone may be at least partially isolated from natural sources, such as human urine. Recombinant follicle stimulating hormone and/or LH may be prepared by methods known in the art. FSH may be produced by recombinant DNA techniques (rFSH), either alone or in a lyophilisate with LH or HCG. Doses of FSH range from 60 to 1500, especially 75 to 225 IU per ampoule lyophilisate (col. 2, line 31-61). A container containing FSH may contain 1 to 1000 µg of FSH. Preferably, the highest reasonable amount of protein possible will be present in a container, since the greater the amount of protein present, generally the more stable the preparation. In one preferred embodiment, a combination of FSH and LH are lyophilized together to form a preparation having therapeutic amounts of both of the selected gonadotropins (col. 3, lines 2-20). The compositions to be freeze-dried preferably contain a non-reducing sugar such as sucrose or trehalose. The incorporation of sucrose, acts to increase the "collapse (or `shrinkage`) temperature" at which the lyophilization of the solution takes place. This increase in temperature simplifies the entire freeze-drying process. The amount of non-reducing sugar present in the solution to be lyophilized will generally be dependent upon the amount of dicarboxylic acid salt stabilizer present. Especially preferred is a solution containing 50 mg/ml sucrose which also yields an optimal lyophilisate in terms of physical characteristics (col. 4, lines 2-41). Also taught are Anti-adsorption agents that are added to the lyophilized composition to prevent adsorbance of the protein to the

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walls of the container in which the compositions are contained, thus preventing a possible decrease in concentration. Certain anti-adsorption agents (e.g. polysorbates) also act as "cryoprotectants" protecting the protein during the lyophilization process. Preferred anti-adsorption agents are nonionic surfactants such as Polysorbate 20, (Tween 20) (especially preferred) Polysorbate 80, (Tween 80) Polysorbate 20, NF is especially preferred. Amounts of Polysorbate 20 sufficient to form a concentration between 0.1 and 0.2 mg/ml in the ultimate solution for use are preferred. Concentrations higher than this tend to lead to oligomer formation, and thus decreased activity (col. 4, line 49 to col. 5, line 8). Another preferred stable lyophilized preparation contains, in admixture, a stabilizer such as a salt of tartaric or aspartic acid, a gonadotropin capable of stabilization by the amount of stabilizer present in the preparation, and a non-reducing sugar. The preparation may further include disodium biphosphate in admixture with the stabilizer, protein, and non-reducing sugar. Especially preferred non-reducing sugars are trehalose and sucrose (col. 5, col. 46-55). A lyophilized composition for recombinant human FSH was made containing 75 IU rFSH, 75 IU LH, 15 mg sodium citrate, 50 mg sucrose, and 0.2 mg polysorbate 20. The preparation is reconstituted with one ml of water for injection (example VIII).

Thus all the limitation of the claims 24-41 and 55 are taught by De Meere et al. On page 9 of the Remarks Applicant argues the rejection over De Meere et al. in view of the new claims. Specifically, the argument is that De Meere does not apply to the invention since De Meere et al. use citric acid in all the combinations. The arguments were carefully considered but not found persuasive because as indicated by Applicant,

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the claims are drawn to formulations that "consist essentially of", which does not exclude other elements like citric acid. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of" for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.") (MPEP 2111.03). The specification mentions citric acid containing buffers (see page 10, lines 1-8 of spec. regarding citric acid as being intended in the specification; see page 14, lines 25-35 regarding "additional additives" and optimization). There seems to be no basis to exclude citric acid since it is mentioned at least 2 times in the specification with regard to buffers and then again on page 10. De Meere emphasizes the citric acid containing formulations for stable formulations that are kept in storage for months, limitation that is not present in the instant claims. The formulations of De Meere et al. contain saccharides which, due to their structure, will perform the stabilizing effect irrespective if De Meere specifically mention it or not. If Applicant wants to specifically exclude the citric acid containing formulation should do so explicitly by choosing the limiting term consisting of.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 42-49 and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Meere et al. (U. S. Pat. No. 5,384,132- cited by Applicant) in view of Skrabanja et al. (EP 0853 945, 07/22/1998).

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The claims are drawn to a freeze dried formulation (or methods of obtaining them) comprising the following ingredients: rFSH, rLH, Tween 20, sucrose, methionine, and a phosphate buffer.

As presented supra, De Meere et al. teach all the elements of the formulations less the methionine.

Skrabanja et al. teach freeze dried formulations FSH produced by recombinant DNA techniques (recFSH), either alone or in admixture with LH. FSH purified from natural sources is generally only partially purified. In a preferred embodiment of the invention the liquid gonadotropin containing formulation comprises as stabilizers a sufficient amount of a citric acid salt, preferably sodium citrate and a sufficient amount of the thioether compound methionine (p.3, line 32 to p. 5, line 21: claims 1-15).

The level of skill in the art at the time that the invention was made was very high, since formulations containing gonadotropins were widely known and used at the time that the invention was made. Adjusting the actual quantities of the ingredient it was therefore considered routine in the art. Therefore it would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the teachings of De Meere et al. and Skrabanja et al. to optimize the quantities with a reasonable expectation of success. The motivation is always present for a person of ordinary skill in the art to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.



Claims 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Meere et al. (U. S. Pat. No. 5,384,132- cited by Applicant) in view of Skrabanja et al. (EP 0853 945, 07/22/1998) and in further view of Franks et al. (WO/2000/067778, 11/16/2000).

The claims are drawn to an article of manufacture comprising- a first container filled with a freeze dried formulation comprising a follicle-stimulating hormone (FSH) or a variant thereof; a luteinizing hormone (LH) or a variant thereof; sucrose, phosphate buffer and methionine and, at least one surfactant selected from the group consisting of including Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), and Tween 80 (polyoxyethylene (20) sorbitan monooleate); and a second container that comprises a solvent for reconstitution, which may be water.

The teachings of De Meere et al. and Skrabanja et al. were presented supra and do not contain, explicitly, two containers.

Franks et al. teach the use of gonadotropins in the treatment of anovulatory women (p.1 , lines 1-2). FSH and/or a biologically-active analogue thereof may be used in the production of the medicament. The IU ratio of LH to FSH is preferably in the range of from 1.5: 1 to 20: 1. More preferably, the ratio is in the range from 1.5:1 to 10:1. A particularly preferred daily dose for such a medicament is 375 IU of r-hLH and 37.5 IU of r-hFSH. (p.7, lines 6-19). Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostatics and solutes which render the formulation

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isotonic with the blood of the intended recipient; aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use p. 9, lines 5-15).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used the freeze dried formulations of De Meere et al. , modified to contain methionine as taught by Skrabanja et al. in the containers of Franks et al. with a reasonable expectation of success since the teachings of Franks are representative of the state of the art in gonadotropin formulations. The motivation to do so is suggested by Franks et al.

### ***Conclusion***

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Christine J Saoud/

Primary Examiner, Art Unit 1647